

REVIEW ARTICLE

State of the art and new horizons in the diagnosis and management of egg allergy

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To cite this article: Benhamou AH, Caubet J-C, Eigenmann PA, Nowak-Węgrzyn A, Marcos CP, Reche M, Urisu A. State of the art and new horizons in the diagnosis and management of egg allergy. *Allergy* 2010; **65**: 283–289.

Keywords

allergens; food allergy; *in vitro* tests.

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Accepted for publication 29 September 2009

DOI:10.1111/j.1398-9995.2009.02251.x

Edited by: Hans-Uwe Simon

Abstract

Egg allergy is one of the most frequent food allergies in children below the age of three. Common symptoms of egg allergy involve frequently the skin as well as the gut and in more severe cases result in anaphylaxis. Non-IgE-mediated symptoms such as in eosinophilic diseases of the gut or egg-induced enterocolitis might also be observed. Sensitization to egg white proteins can be found in young children in absence of clinical symptoms. The diagnosis of egg allergy is based on the history, IgE tests as well as standardized food challenges. Ovomucoid is the major allergen of egg, and recent advances in technology have improved the diagnosis and follow-up of patients with egg allergy by using single allergens or allergens with modified allergenic properties. Today, the management of egg allergy is strict avoidance. However, oral tolerance induction protocols, in particular with egg proteins with reduced allergenic properties, are promising tools for inducing an increased level of tolerance in specific patients.

Prevalence

IgE-mediated food allergy is common among children and egg white, together with milk and peanuts, is one of the foods most frequently incriminated below the age of 3 years. The estimated prevalence of egg allergy has been reported to vary, depending on method or definition. Self-reported prevalence values of egg allergy of up to 7% have been demonstrated, while challenge-confirmed egg allergy has shown lower estimates, up to 1.7% (1). An estimated point prevalence of 1.6%, confirmed by challenge, was reported from Norway and Denmark (2, 3), and a similar prevalence of 1.3% was reported from the United States (4). Egg allergy also accounts for a high prevalence in childhood in France and Japan (5, 6). Egg allergy is the most common food allergy in children with atopic dermatitis. Egg allergy was found to be present in about two-thirds of children with positive food challenges made for allergy work-up of atopic dermatitis (7).

Symptoms (clinical presentation)

Initial allergic reactions to egg are usually observed during the first year of life. The most common symptoms are

IgE-mediated erythema, urticaria and eczematous rash occurring in 90% of the children (8). Furthermore, gastrointestinal symptoms, abdominal pain and vomiting (mostly in conjunction with other immediate-type symptoms) occur in 40–50% of cases following egg ingestion. In addition, egg is one of the most common food allergens in allergic eosinophilic esophagitis (AEE) and allergic eosinophilic gastroenteritis (AEG) that might be IgE-mediated, cell-mediated or both (9). AEE is seen most frequently during infancy through adolescence, whereas AEG can occur at any age, including young infants. Food protein-induced proctocolitis and food-induced enterocolitis, also reported to be egg-induced, are other gastrointestinal disorders and appear to involve a non-IgE, cell-mediated mechanism (10, 11).

Anaphylactic reactions to egg are not commonly reported, even in children. However, the reaction severity has been associated with asthma, suggesting that asthma care should be a critical target for supervision of children with food allergy (12). In rare cases, egg has caused fatal reactions because of anaphylaxis (13).

Ingestion of cooked or baked egg can be tolerated by some children who react to raw egg, whereas other children react both to raw as well as heated egg (14–18).

Egg white components

Egg white is the major source of allergens in egg. Egg white contains 23 different glycoproteins, most of which have been purified. Ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovomucoid/transferrin/conalbumin (Gal d 3) and lysozyme (Gal d 4) have been identified as the major allergens (Table 1) (19). Although ovomucoid comprises only 10% of the total egg white protein, it has been shown to be the dominant allergen (19, 20). Ovomucoid has several unique characteristics, such as stability against heat and digestion by proteinases. It also appears to be allergenic in minute quantities.

Sensitization

Initial sensitization to food is generally accepted to take place via the gut mucosa or cutaneous exposure (21). Sensitization to food in infants is often transient and low levels of IgE antibodies to egg can occur without any symptoms (22), highlighting the fact that allergen-specific IgE is a marker of allergic sensitization and not of allergic disease. Reactions occurring on first known ingestion or skin contact with egg are not uncommon (23). In a prospective study of 107 young children who not previously ingested egg but were sensitized to egg white, oral food challenges to egg were performed at a median age, 15 months (range; 12–24 months). The egg challenge resulted in an immediate or early reaction (within 6 h) in 56/107 (52.3%) children (24). The presence of IgE antibodies to egg has been demonstrated in infants with atopic dermatitis before the introduction of egg into the diet (24, 25). Sensitization may thus theoretically occur either by transplacental transfer of egg allergen (26) or through breast milk (27). In addition, experience with occupational asthma to inhaled egg proteins that may be followed by breakdown in previously established oral tolerance to ingested egg, suggests a possible inhalation route for primary sensitization to egg allergens (28, 29).

The pattern of allergic sensitization in a large cohort of infants with atopic eczema, participating in an international study multicenter was recently published and showed a predominance of sensitization to egg in each country, with a global rate of sensitization to egg white of 42% (30). The pattern of sensitization to egg white in the individual countries was paralleled by the pattern of sensitization to peanut.

Sensitization to egg white is considered to be a risk factor for development of peanut allergy; 20% of children with AD and egg white sensitization will ultimately develop peanut allergy. In an ongoing clinical trial, headed by Dr G. Lack in London, investigating prevention of peanut allergy [LEAP study; Learning Early About Peanut allergy], infants between the ages of 4 and 10 months and with AD and detectable serum egg white IgE antibody levels are randomly assigned to peanut avoidance until 3 years of age or to early introduction of a peanut-containing snack three times per week (equivalent to about 6 g of peanut protein per week). The primary endpoint of the study is the proportion of children who develop peanut allergy by age 5 years in each study group. The study will reach completion in 2013.

A strong association between sensitization to egg during infancy and sensitization to inhalant allergens later in childhood has been observed by several groups (31–35). Sensitization to egg in infancy, and particularly in combination with atopic dermatitis, should thus be considered a risk marker for predicting future inhalant allergy. The mechanism of this association has not been elucidated.

Common vaccines, such as influenza vaccine, that are cultured in fertilized chicken eggs may contain small amounts of egg allergen, and immunization with these vaccines might cause adverse effects in children with egg allergy (36). Egg allergy is therefore still considered a contraindication to immunization against influenza, particularly in individuals with a history of egg anaphylaxis. However, it has been clearly demonstrated that minute amounts of egg proteins possibly present in the MMR vaccine do not provoke allergic reactions in egg-allergic individuals, implying that this vaccine is not contraindicated in egg-allergic individuals (37).

Diagnosis

Challenge

An accurate history is the key element in the diagnostic process of egg allergy. The double-blind placebo-controlled food challenge (DBPCFC) test remains the golden standard for the confirmation of food allergy although, in clinical practice and especially in infants, open challenges are useful. Challenge methods often vary from study to study and challenge availability varies from country to country. Standardized guidelines would facilitate comparison of the

Table 1 Major egg white allergens

Allergen	Common name	Constitute* (%)	Mw (kDa)	pI	Carbohydrate (%)	IgE binding activity		Allergenic activity	Test code (<i>in-vitro</i> tests)
						Heat-treated	Digestive enzyme-treated		
Gal d 1	Ovomucoid	11	28	4.1	~25	Stable	Stable	+++	f233
Gal d 2	Ovalbumin	54	45	4.5	~3	Unstable	Unstable	++	f232
Gal d 3	Ovotransferrin/conalbumin	12	76.6	6.0	2.6	Unstable	Unstable	+	f323
Gal d 4	Lysozyme	3.4	14.3	10.7	0	Unstable	Unstable	++	k208

*Percent of egg white proteins.

outcome and results between studies. A Position Paper for this purpose has been presented by the European Academy of Allergology and Clinical Immunology (38). Challenge tests always imply a potential risk to the allergic child and should thus only be performed by trained allergists in clinics with adequate facilities. Besides, challenge tests are time-consuming and not considered practical in the primary care setting. The diagnosis is therefore often assessed by quantitative IgE tests but always needs to be correlated to a convincing history (39). It should be emphasized that if a child tolerates egg in the diet on a regular basis without any immediate reaction, then this child is not egg allergic, even if high levels of egg white-specific IgE antibody are detected in serum. In clinical practice, food challenges are used both for initial diagnosis as well as monitoring of food allergy resolution. This is already the trend in milk and egg allergy but needs further support for everyday practice.

Skin prick tests

Skin prick tests (SPT) are frequently used in screening for egg-specific IgE and should be performed by trained personnel. The diagnostic accuracy of SPTs is dependent on the quality of the extract, which should be standardized. In children with atopic dermatitis and egg allergy, SPT shows a good sensitivity and NPV, but poor specificity and PPV (40). As a consequence, a negative test essentially excludes an IgE-mediated egg allergy, whereas a positive test does not predict clinical reactivity accurately. Few studies correlated the results of the prick skin test with the outcome of an oral egg challenge. In a study by Sporik et al. (41), positive skin reactions to egg ≥ 7 mm (mean wheal diameter) were associated with an adverse reaction on a formal open challenge, indicating that a wheal diameter equal to or greater was 100% specific in defining the outcome of challenge. For 3 mm diameter, the specificity was reduced to 70% for egg, and positive challenges were observed in children with a negative skin reaction.

In vitro IgE tests

IgE antibodies to egg white proteins can be measured in serum by standardized assay systems, used in clinical routines. As for SPT, the quality and performance criteria for the assay need to be considered. The test is principally dependent on the egg allergen preparation, composition, quality and stability. Commercially purified egg white single proteins often contain significant quantities of contaminating protein, which may lead to erroneous interpretation of test results (19).

In vitro IgE antibody tests provide standardized, quantitative measurements of egg-allergen-specific IgE, and a relation between the concentration of egg-specific IgE antibodies and the probability of reaction during an ingestion food challenge can be determined. Threshold values of egg-specific IgE (cutoff values) to predict the outcome in challenge have been defined in several studies, showing various predictive values. Crespo et al. (42) challenged children with egg allergy after 2.5 years of egg elimination, and the outcome of the

challenges were correlated with the egg-specific IgE antibody levels. A likelihood ratio of 6.3, if the concentration of egg-specific IgE was 1.2 kU_A/l, made the investigators draw the conclusion that challenges could be delayed in children with egg-specific IgE concentrations greater than 1.2 kU_A/l. The studies by Sampson (43) suggested the diagnostic decision point for egg white IgE to be 7 kU_A/l, with 95% of the children having a clinical reaction. A similar value, 7.4 kU_A/l, was recently reported by Ando et al. (44). Although different values have been demonstrated in other studies, the predictive cutoff values are constantly lower in small children and increasing by age (8, 45–48). For children under 2 years of age, egg white IgE level ≥ 2 kU_A/l has 95% PPV (49).

The range of cutoff levels observed might depend not only on differences in age, but also on the type of symptoms, other clinical characteristics of the cohorts such as prevalence and/or various challenge procedures and the type of food given during the challenge. Future studies utilizing patients with well-characterized clinical phenotypes and with standardized challenge protocols, including foods preparation, should give better comparable results and useful predictive information (50).

In children with low levels of egg-specific IgE, those with the smaller SPT responses to egg were shown to be more likely to pass a challenge test to egg than children with larger wheal responses. In children with egg white IgE levels < 2.5 kU_A/l, the skin test wheal diameter of egg white commercial extract equal or smaller than 3 mm was associated with a 50% pass rate during the supervised oral egg challenge. Thus, on these occasions, a combination of the two tests might provide additional information to the clinician in determining the timing of egg challenge (51).

The studies mentioned earlier set cutoff levels for the diagnosis of egg allergy and did not evaluate the egg-specific IgE levels in relation to the severity of the challenge reaction. This was recently investigated by retrospectively reviewing clinical data on symptoms at a standardized oral food challenge to egg and egg-specific IgE levels. Analyses showed statistical differences in egg-specific IgE levels for patients with severe, moderate or absent reactions at challenge, highest for patients with severe reactions and decreasing with the severity of reaction.

This indicates that the level of egg-specific IgE might be a help to assess the potential risk of a reaction to egg (48).

Ovomucoid in the diagnosis of egg allergy

Ovomucoid is heavily glycosylated and contains three well-separated domains, which have been investigated with regard to allergenicity (52). Each domain bears unique epitopes that are recognized by IgE antibodies from egg-allergic patients. Analysis of sera from egg-allergic patients showed that IgE antibodies reacted with all three domains but significantly more to the second ovomucoid domain (20). However, further investigations could demonstrate a higher IgE-binding to the pepsin digests of ovomucoid in egg-allergic patients who did not outgrow their allergy, compared to patients who developed tolerance (53). Previous studies have suggested that

the allergenicity could be explained by the fact that ovomucoid demonstrates a higher stability against protease digestion and heat compared with other egg white components (14, 19). Significant differences in IgE antibodies to ovomucoid were found in patients, depending on the reactivity to raw and cooked eggs, where low levels of IgE antibodies to ovomucoid were associated with tolerance to cooked eggs (14). Furthermore, quantification of ovomucoid antibodies could be useful in guiding the physician in the decision whether to perform a challenge or not. Recently published data suggest that a concentration of IgE antibodies to ovomucoid higher than approximately 11 kU_A/l (positive decision point) indicates a high risk of reacting to heated (as well as raw) egg. At the same time, a concentration lower than approximate 1 kU_A/l (negative decision point) means that there is a low risk of reaction to heated egg, even if the patient might well react to raw egg (44).

New diagnostic tools for egg allergy

Recent advances in technology, improved purified allergens and specific epitopes open up new opportunities and better defined diagnosis of food allergy. Component-resolved diagnostics using microarray technology has recently been evaluated in the diagnosis of egg allergy. The clinical performance of an allergen microarray, containing a panel of clinically relevant egg components, has been evaluated for IgE detection in children with challenge-proven egg allergy. The results showed performance characteristics comparable to current diagnostic tests, both *in vitro* IgE-test and SPT (54). The advantages of the microarray assay allow for characterization of several allergen components simultaneously. Furthermore, the small volume obtained by capillary blood sampling makes the microarray assay suggestive for testing in small children.

Point-of-care (POC) tests for small children, requiring small volumes of capillary whole blood and with results

within 30 min, could be particularly suitable in primary care settings. A new POC test with a panel of ten allergens, including egg white, has recently been evaluated and published, with an overall sensitivity and specificity of 92% and 97%, respectively (55). Measurements of IgG₄ and the ratios of IgE/IgG₄ have also been shown to be useful in following the development of tolerance and outgrowing of egg allergy in the research studies (56, 57). However, at this time, measurement of IgG₄ has not been validated sufficiently to be used in clinical practice.

Management/therapy

Today, the standard therapy for egg allergy is strict avoidance, access to self-injectable epinephrine and adequate pharmacotherapy in the event of an accidental ingestion. Basic food, such as egg, is widely used in many processed foods and difficult to avoid. This difficulty in egg avoidance and the risk of dietary failures have been shown to affect the quality of life for egg-allergic children as well as their families (58).

Oral desensitization to different foods has earlier been reported with a limited number of patients and various results of tolerance achievement (59, 60). In recent years, more promising articles have been published on achieving clinical tolerance to egg by oral immunotherapy (OIT), or sometimes called specific oral tolerance induction (SOTI).

Food allergy seems to result in a failure to establish or maintain oral tolerance (61). In order to achieve tolerance, the offending food is administered orally in small doses, which are increased slightly up to an amount equivalent to the usual daily oral intake. Thereafter, the food is given daily in a maintenance dose (62, 63). New preparations of heated and ovomucoid-reduced egg white, which is hypoallergenic enough to eat for approximately 95% of egg-allergic subjects, are currently under investigation and might be effective and safe for patients under OIT (Fig. 1). The individual pattern

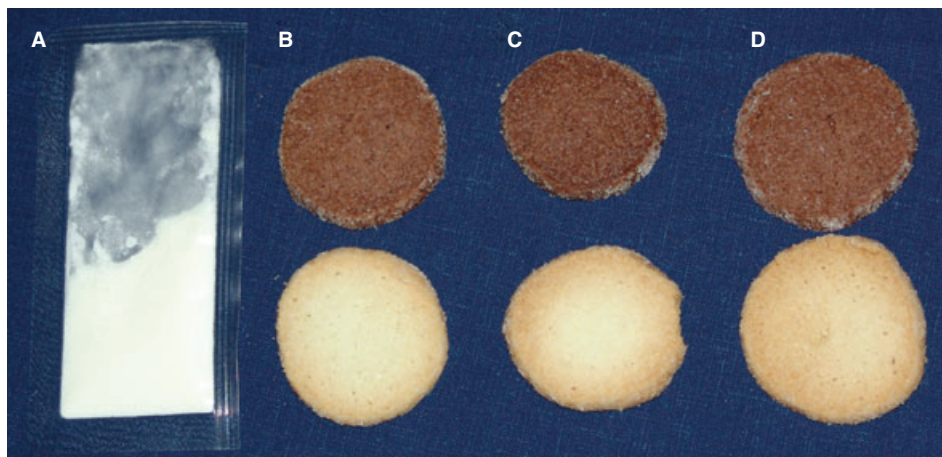


Figure 1 (A) Freeze-dried egg white, (B) Cookie including heated & ovomucoid-reduced egg white, (C) Cookie including heated egg white, (D) Cookie without egg white.

of clinical reactions seems to vary between patients and type of allergen. In some patients who obtained tolerance by OIT, the allergic symptoms were found to re-occur after a period of avoidance, indicating a short-term and not lifelong tolerance to egg (62, 64). As a consequence, regular egg ingestion might be necessary to maintain the established tolerance for those patients.

Children with successful oral immunotherapy to egg were shown to have lower baseline levels of IgE antibodies to egg compared to nonresponding children. In addition, the levels of egg-specific IgE decreased over time in children with successful OIT. However, this study also showed that egg-specific IgE decreased in children who developed natural tolerance during elimination diet (63).

Furthermore, other studies have demonstrated an increase over time in IgG and IgG₄ antibodies to egg during oral immunotherapy (61, 65, 66).

Immunologic changes associated with ingestion of extensively heated egg in children with egg allergy were recently published by Lemon-Mulé et al. (56). Children reacting to heated egg had significantly larger egg white-induced SPT, greater levels of IgE antibodies to egg white, ovalbumin and ovomucoid and higher OVA-IgE/IgG₄ and OVM-IgE/IgG₄ ratios, compared with children tolerant to heated and unheated egg. Continued ingestion of heat-treated egg for tolerant children showed a decrease in OVA-IgE/IgG₄ and OVM-IgE/IgG₄ ratios from baseline at 3, 6 and 12 months, respectively. These results suggest that ingestion of heated egg by tolerant children might hasten the development of tolerance to unheated egg. The authors found that only extremely increased levels of IgE antibodies to ovomucoid ($> 50 \text{ kU}_A/\text{l}$) were highly predictive of heated egg reactivity. This might be explained by the so-called matrix effect (67, 68), because of the fact that the heated egg used in the study was baked with wheat matrix. Kato et al. (69) previously showed a decreased solubility of ovomucoid when egg was mixed with wheat flour and wheat gluten and heated, suggesting that ovomucoid forms complexes with gluten leading to aggregation and insolubilization.

Resolution/persistence

The prognosis of egg allergy in young children is generally good and shown to resolve in 50% by age 3 years and in 66% by age 5 years (49). However, results from a recent study suggest a longer duration of allergy, predicted resolution in 4% by age 4 years, 12% by age 6 years, 37% by age 10 years and 68% by age 16 years. Moreover, children with egg-specific IgE greater than $50 \text{ kU}_A/\text{l}$ were unlikely to develop egg tolerance (70).

Monitoring egg-specific IgE levels has been found to be useful in predicting when patients will develop clinical tolerance. A relationship between the degree of decrease in egg-specific IgE concentration over time and the probability of developing tolerance has been demonstrated, showing that a greater decrease in egg-specific IgE levels over a shorter period was indicative of a greater likelihood of tolerance development (71). Application of this model might help the

clinician in the timing of challenge and in offering information to the patient and the family regarding the prognosis of the allergic disease.

Significantly higher levels of specific IgE antibodies to ovomucoid were demonstrated in children with persistent egg allergy. Children with high levels of IgE antibodies binding to pepsin-treated ovomucoid were thus less likely to outgrow their egg allergy compared to children who developed tolerance (53). In addition, sera from children with persistent egg allergy recognized more linear epitopes on ovomucoid. Four sequential IgE-binding sites on ovomucoid have been identified, differentiating children with persistent egg allergy from those with transient egg allergy (72). The presence of IgE antibodies to specific sequential epitopes may therefore be useful as a screening tool for persistent egg allergy.

High ratios of IgG₄/IgE antibodies to ovalbumin were also associated with a faster achievement of clinical tolerance in egg-sensitized children with eczema, who had been able to introduce egg in their diet. As a consequence, IgG₄/IgE ratios may be a valuable marker for identifying sensitized children able to continue with allergen exposure (57).

Future perspectives

The goals for the future are

- Prediction of tolerance when the diagnosis of egg allergy has been established:
 - by measuring antibody titers of specific egg white proteins in various forms (heated or unheated).
 - by determining whether combinations of tests to specific egg white proteins in various forms could predict tolerance to eggs.
 - by determination of IgE/IgG ratios.
- Efficient induction of tolerance to egg in egg-allergic individuals:
 - by studying efficient tolerance induction protocols with heated and partially heated egg-containing food products.
 - by establishing safe and efficient mucosal and systemic immunotherapy protocols.
- Prevention of development of egg allergy or progression to allergic symptoms in high risk individuals for allergy:
 - by identifying at-risk individuals with appropriate (egg-specific) tests.

In conclusion, egg allergy is not only most common in children suffering from food allergies, but sensitization to egg protein is a complex, only partially characterized phenomenon found in allergy-prone individuals. Addressing various aspects of egg allergy and antibody response to egg sensitization will allow most fascinating studies with a direct impact in order to prevent allergic manifestations in childhood.

Acknowledgments

This article is based on a scientific workshop regarding the diagnosis and management of egg allergy made possible through an unrestricted educational grant from Phadia.

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